DOCUMENT-IDENTIFIER: US 6585975 B1
TITLE: Use of Salmonella vectors for vaccination against helicobacter infection

Drawing Description Text (3):
FIG. 2A is a graph showing the urease-specific serum antibody (IgG2a) response of mice that were mucosally primed with S. typhimurium-vectored urease, followed by parenteral boosting with urease and alum.

Drawing Description Text (4):
FIG. 2B is a graph showing the T helper phenotype (IgG1/IgG2a ratio) of mice that were mucosally primed with S. typhimurium-vectored urease, followed by parenteral boosting with urease and alum.

Drawing Description Text (5):
FIG. 3A is a graph showing protection against Helicobacter infection in mice that were mucosally primed with S. typhimurium-vectored urease, followed by parenteral boosting with urease and alum.

Drawing Description Text (6):
FIG. 3B is a table showing protection against Helicobacter infection in mice that were mucosally primed with S. typhimurium-vectored urease, followed by parenteral boosting with urease and alum, as log .sub.10 reduction in comparison to a no treatment control group.

Detailed Description Text (29):
As is noted above, the method of the invention involves mucosal (e.g., oral, intranasal, intragastric, pulmonary, intestinal, rectal, ocular, vaginal, or urinary tract) administration of a Salmonella vector including a nucleic acid molecule that encodes a Helicobacter antigen, followed by parenteral (e.g., intramuscular, subcutaneous, intradermal, intraepidermal, intravenous, or intraperitoneal) administration of a Helicobacter antigen, preferably in association with an adjuvant. The antigen used in the mucosal prime can be different from, cross-reactive with, or, preferably, identical to the parenterally administered antigen. Preferably, the mucosal administration step primes an immune response to an antigen, and the parenteral administration step boosts an immune response to the antigen. Also included in the invention are vaccination methods involving parenteral priming and mucosal boosting (e.g., with a Salmonella vector including a nucleic acid molecule encoding a Helicobacter antigen), and parenteral administration of a Salmonella vector including a nucleic acid molecule encoding a Helicobacter antigen.

Detailed Description Text (31):
In one example of an immunization regimen that can be used, a patient is primed with two doses of an attenuated Salmonella vector (e.g., S. typhi CVD908-htrA or CVD908, or S. typhimurium BRD509 or BRD807) expressing an antigen (e.g., urease from plasmid pHUR3, pHUR4, pNUR3, or pNUR4) on days 0 and 21, and then parenterally boosted on day 51 or later with an antigen (e.g., urease) and an adjuvant (e.g., alum). The details of construction of pHUR3 and pNUR3, which each include an ampicillin resistance gene, are described below. pHUR4 and pNUR4 are constructed by removing the ampicillin resistance gene from pHUR3 and pNUR3, respectively, by digestion with the restriction endonuclease RcaI, and cloning into the digested vectors a kanamycin resistance gene that can be obtained from plasmid pUC4K (Pharmacia) by digestion with EcoRI.

Detailed Description Text (57):
Inbred Balb/C mice were immunized by the intragastric route with live, attenuated Salmonella typhimurium (1E10 CFU/ml) expressing urease apoenzyme on day 0 (FIG. 1). Animals were boosted twice on days 21 and 35 with 10 .mu.g soluble, recombinant urease plus aluminum hydroxide (200 .mu.g) by the parenteral route. Fourteen days later, serum antibody responses to urease were

measured. Controls included: (1) prime-boost with the Salmonella parental control strains (BRD509 .DELTA.aroA/.DELTA.aroD (Strugnell et al., Infection and Immunity 60:3994-4002, 1992) and BRD807.DELTA.aroA/.DELTA.htrA (Chatfield et al., Microbial Pathogenesis 12:145-151, 1992)) minus the urease construct, (2) mucosal priming with LT in place of Salmonella (gold standard), and (3) parenteral immunization with urease plus alum alone. Attenuated S. typhimurium (.DELTA.aroA/.DELTA.aroD) expressing urease under the transcriptional control of either an htrA promoter (pHUR3) or the nirB promoter (pNUR3) induced an elevated IgG2a response against urease that was greater than the gold standard using LT-Alum (FIG. 2A). A comparable response to LT-Alum was induced with S. typhimurium (.DELTA.aroA/.DELTA.htrA) carrying the same urease constructs (FIG. 2A). Analysis of the IgG1/IgG2a ratio demonstrated the induction of a Th1 response with the double aro mutant, and a more balanced response with the .DELTA.aro/.DELTA.htrA mutant strain (FIG. 2B). Urease-specific antibody in FIG. 2A is expressed as EU/ml on a logarithmic scale and median response is indicated by the bar.

Other Reference Publication (23):
Lee et al., "Immunization of Rhesus Monkeys with Mucosal Prime, Parenteral Boost Strategy Protects against Infection with Helicobacter pylori," Abstract-Vaccine 17:3072-3082 (1999).